NON TECHNICAL ABSTRACT

Stem cells obtained from the bone marrow or peripheral blood of one individual, can be used to cure leukemia in another individual as part of an "allogeneic" stem cell transplantation (frequently called a bone marrow transplant), The anti-leukemic effect of a stem cell transplant arises from two sources. First, the high dose chemotherapy (& or radiation) that is administered prior to transplanting the stem cells may kill more leukemia cells than could be killed with conventional doses of chemotherapy. Secondly, the transplanted cells may kill leukemia cells via the immune system. This is called the graft-vs.leukemia (GVL) effect. The ability to give leukemia patients the chance to benefit from the potentially curative GVL effect is limited by the complications associated with stem cell transplantation. T-lymphocytes, the same type of cell responsible for generating the GVL effect, can also cause severe damage to tissue and organ systems in the host. This is called graft-vs.-host-disease (GVHD). GVHD occurs very frequently and is severe in about 40% of allogeneic transplants. It is standard practice to try to prevent GVHD by suppressing T-cell function, and, if prevention is not successful other drugs that further suppress the immune system are utilized. These current therapies are frequently unsuccessful, have many toxicities, and increase the risk of severe or fatal infections. About 25% of patients undergoing allogeneic transplantation die as a consequence of GVHD or its therapy. The risk of GVHD restricts transplantation to about 50% of patients that have a donor that "matches".

This proposal seeks to test if a new approach to treating GVHD can be more successful than current therapies. As discussed above current GVHD therapy suppresses the function of all T-cells, but does not eliminate the T-cells causing the GVHD. Our strategy aims to selectively eliminate the GVHD causing T-cell while sparing other T-cells and the immune system. We propose to use a retrovirus to introduce a "suicide" gene (Herpes Simplex virus thymidine kinase, HSV-TK) into the T-cells collected from the donor before they go into the host. If these T-cells cause GVHD a drug called ganciclovir is given to the patient. The gene modified T-cells that are causing the GVHD, which carry the HSV-TK gene, convert this drug to a toxic form and die. With the selective death of the GVHD causing T-cell the GVHD resolves. The advantage is that uninvolved T-cells are not affected so there is no immunosuppression associated with this GVHD therapy. Therapy is short and toxicity from the ganciclovir is likely to be significantly less than with current long-term immunosuppressive GVHD therapies. If this strategy reliably controls GVHD then patients without perfect matches would also be able to undergo transplantation and potentially benefit from the GVL effect. If successful, the benefits of this strategy are that it would create a more effective and less toxic therapy for GVHD and it would allow more patients to be cured by the GVL effect by removing current barriers to transplant.